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Steps to prevent and respond to an H5N1 epidemic in the USA | Nature Medicine

Steps should be taken now to prevent an epidemic of H5N1 in humans and prepare for an outbreak should it occur.

The spread of H5N1 avian influenza among US dairy herds raises the possibility that the virus could evolve to enable transmission between humans, cause severe disease in humans and spur a major epidemic. At the time of writing, there has been no evidence of efficient human-to-human transmission (a prerequisite for an epidemic) and, despite the roughly 50% mortality rate seen globally, only 2 of the more than 60 people diagnosed in spillover infections in the USA and Canada experienced severe illness or death.

H5N1 may never become a bigger threat, but there are many unknowns with the virus and there is a risk that it could evolve in dangerous ways. The ongoing circulation of H5N1 among cows, especially in human influenza season, heightens the chance that, through mutations or reassortment, a strain that is capable of human spread and more severe disease could abruptly emerge.

Several steps should be taken now to reduce the chance for such viral evolution to occur and to prepare strategies that could efficiently control spread if a more virulent strain with sustained human transmission emerges.

Preventing viral adaptation

As of 6 January 2025, over 900 dairy herds in 16 US states and poultry in 50 states have been confirmed to have had H5N1 infections1. Owing to limited testing, the true extent of spread in animals and humans remains unclear. Some farm owners have been resistant to testing owing to concerns of financial loss. Farm workers, many of whom are undocumented, are often reluctant to get tested because of fears of losing work and possible immigration issues. A recent serosurvey found that 7% of dairy workers in Colorado and Michigan had serological evidence of recent infection, suggesting that many more workers than reported have been infected2.

For H5N1 to cause a human epidemic, the virus would need to evolve to become capable of causing human-to-human spread (transmissibility). If spreading widely, even the seemingly low rate of severe disease seen so far would be enough to cause a major crisis. The virus could also evolve to more frequently cause severe illness (pathogenicity). So far, there has been no evidence of efficient or sustained human transmission. At least four specific mutations have been identified that may facilitate human-to-human spread. As yet unknown mutations may also exist and increased transmissibility may become possible with as little as a single mutation3,4. Multiple concerning mutations have already been identified in viruses isolated during this outbreak5.

Since 1997, about half of H5N1 infections have resulted in death. By contrast, all but 2 of the more than 60 affected individuals in this outbreak have experienced mild illness, most commonly with conjunctivitis5. The global case fatality rate may be inflated, because mild infections may have gone undetected. An additional consideration is that these

undetected. An additional consideration is that these infections were caused by viruses from clades different than the clade 2.3.4.4b H5N1 viruses currently circulating. Although some infections of clade 2.3.4.4b viruses in other countries caused severe illness and death, the strains from this clade spreading in the USA, particularly genotype B3.13 circulating among dairy cows, may be, thus far, less virulent5,6. In the two cases of severe illness, both individuals were infected with genotype D.1.1 strains found in birds5.

Besides strain differences, H5N1 infections in the USA may have also been mild owing to immunity conferred by past influenza infections and differences in viral receptor affinity. Human lower respiratory tract and conjunctival cells have α2,3-linked sialic acid receptors similar to avian and bovine mammary gland tissues (where H5N1 is found in high loads)6. Viral affinity for this receptor type may explain why dairy workers get conjunctivitis from infected milk splashing into their eyes, whereas inhalation of infected aerosols in viral loads sufficient to cause pneumonia may be less likely to occur.

These explanations are inconclusive and much remains unknown about H5N1. In a recent experiment, H5N1 isolated from an infected farm worker in Texas replicated efficiently in human respiratory cells and was highly lethal in ferrets, an animal often used to model human influenza7. There are also reports from California describing increased mortality among infected dairy cows and insufficient recovery of milk production after infection8.

Although circulating H5N1 strains may never become transmissible and deadly in humans, H5N1 has already evolved these abilities in several animals, including multiple mammalian species6. Viral evolution can be accelerated by viral reassortment, a process in which genomic segments are swapped between viruses. Reassortment is particularly likely to occur during human influenza season when people and some animals, such as pigs, can be simultaneously co-infected with H5N1 and seasonal human influenza viruses (such as H3N2 or H1N1). The best way to preclude an H5N1 epidemic is to dampen the odds for such evolution by preventing infections in farm workers, eliminating viral circulation in cows and expanding genomic and human surveillance.

Protecting farm workers

In July 2024, the Centers for Disease Control and Prevention (CDC) launched an initiative to reduce the risk of co-infections by providing at-risk farm workers with free seasonal influenza vaccination. Uptake has not been publicly reported, but efforts to increase coverage should be redoubled. More evidence is also needed on the risks and benefits of offering farm workers an H5N1 vaccine, which provides an unclear degree of protection.

Sealing the human–animal interface from spillover infections could also reduce chances for H5N1 to reassort or otherwise adapt to humans. Farm workers, however, have not been reliably wearing personal protective equipment (PPE) even though it has been freely offered. This is, in part, owing to the intense heat of their working conditions. PPE options exist that could provide ocular, respiratory and full-body protection from both the virus and the heat, including powered air purifying respirators and cooling garments9. At the time of writing, the weather in many dairy farming locales is cooler than in previous months, making conventional PPE also less

onerous. Infection control experts should optimize farm workflows and, with workers' input, determine practical, yet sufficiently protective, options.

Eliminating circulation among dairy cows

Although persistent H5N1 circulation among any animal reservoir poses a risk, viral spread among dairy cows is uniquely concerning, as cows are kept in large numbers on industrialized farms with frequent, close human contact. If H5N1 becomes endemic among cows it may further evolve mammalian adaptations, cause sporadic spillover infections of humans and other high-risk animals and remain an ever-present threat to become transmissible and virulent among humans.

Stopping bovine circulation has proven difficult owing to the lack of buy-in from farm owners. In July, Colorado mandated weekly testing of bulk milk tanks on all dairy farms and subsequently uncovered H5N1 in about three-quarters of the state's herds. Herds testing positive were isolated and required two consecutive negative tests to be cleared. With this approach, Colorado was able to clear all of its farms of H5N1 circulation.

Until recently, only Massachusetts and California had pursued analogous mandates. In December, the United States Department of Agriculture (USDA) launched the National Milk Testing Strategy to screen milk at regional siloes and support states in implementing bulk milk sampling programs to pinpoint infected herds10. This initiative just started and it is too early to gauge its impact on slowing H5N1 circulation. The program is currently operating in 28 states accounting for about two-thirds of US milk production, potentially missing states in which H5N1 may be present, but not yet detected owing to limited testing.

If this strategy does not work effectively, and on-farm testing similar to Colorado is not possible in other states, creative workarounds to detect viral circulation may be needed. One potential solution is to expand wastewater surveillance by sampling as close to dairy farms as legally possible and using genomic sequencing to detect the presence of H5N1 (ref. 11). A team from the Texas Public Health Institute recently described a two-year ten-city proof of concept for using sequencing in this manner to detect H5N1 in wastewater12. Their protocol or a similar one could be scaled to identify H5N1 circulation throughout the country.

Genomic and human surveillance

Independently of detecting localized viral spread, genomic sequencing should be regularly performed whenever H5N1 is found in bulk milk, individual herds, human infections and wastewater surveillance efforts. Sequencing would enable monitoring for the potential accumulation of human-adaptive mutations and phylogenetic analysis to elucidate the likely species source5.

In light of evidence from serosurveys of asymptomatic or mildly symptomatic infections, the CDC now recommends that anyone working with animals known to be infected should be screened for H5N1, even if they do not have symptoms, and offered antivirals if they had high-risk contact without wearing PPE2. This screening should ideally be expanded to all people with similar proximity to dairy cows, poultry and wild birds even if these animals have not yet been tested for H5N1. Anyone with relevant exposures who develops

symptoms should also be tested for H5N1 and seasonal influenza. Detecting these human infections could enable steps to prevent co-infection and potential reassortment, help provide timely care and monitor potential changes in viral pathogenicity or transmissibility.

Disinfection and indoor air cleaning

Even with these steps, a human transmissible, virulent strain may still emerge and begin spreading widely. Several measures could be considered and prepared in advance of such a scenario. Many of these preparations are not specific to H5N1 and would offer preparedness for whatever epidemic comes next.

Even without genomic data on the virus or biomedical countermeasures such as vaccines, 'engineering controls' could biophysically help slow transmission. H5N1 seems to mainly transmit through secretions, especially milk from dairy cows, and via farm machinery, vehicles and possibly the clothing of farm workers6. Protocols for hand hygiene and disinfecting surfaces in an emergent epidemic should be created and shared with schools, workplaces and other settings now, similar to earthquake protocols. If a virus with epidemic potential emerges, instead of panic, these instructions could be put into practice and refined as further information becomes available.

H5N1 evolving an ability for airborne transmission would pose the greatest risk for a widespread pandemic and could be mitigated by implementing ambient air cleaning in all shared indoor spaces, such as workplaces, schools and homes. The CDC recommends five or more air changes per hour, which could be achieved without costly HVAC systems by using portable air cleaners (including those made from off-the-shelf box fans and filters) that could be scaled quickly and feasibly. The CDC target could be reached in a typical classroom for US$250 (ref. 13). One study shows that short-range accumulations of infectious aerosols could be effectively disbursed by ceiling fans, which are already common and could be readily scaled14. Additional techniques are needed when ceiling fans are not feasible. Given that many viruses exhibit overdispersion, further research is also needed to determine the likely amounts of pathogen released by high-emitting infectors (sometimes known as superspreading), as filtration or ventilation should be matched to these superspreaders. The widespread implementation of air filtration would also enable filters in public settings to be sampled and sequenced to monitor for H5N1 circulation13.

Lab testing and rapid self-testing

Preparations should be made so that labs nationwide, including public health, academic and commercial, could be quickly operationalized to test for H5N1. A few commercial laboratories have already started offering H5N1 testing.

Tiers of testing could be activated based on how well transmission chains and contacts are known. If most transmission chains remain tracked via contact tracing, then only testing sufficient for screening these contacts is needed. If infections arise among people with no links to known cases, anyone with suspicious symptoms in areas with possible transmission would need to be tested and a wider swath of labs activated. If asymptomatic and presymptomatic spread is occurring among unknown transmission chains, then, as with COVID-19, frequent screening of all people in affected areas would be necessary, which could be best accomplished with rapid self-tests. The development of such tests, ideally more

rapid self-tests. The development of such tests, ideally more accurate molecular tests such as loop-mediated isothermal amplification, should be initiated now so that their validation and production could be moved forward quickly if they become necessary. In the interim, rapid antigen tests for influenza A (of which H5N1 is a subtype) are already widely available. Though these tests cannot distinguish H5N1 from seasonal influenza A infections, they could be used as a stopgap for presumptive diagnosis and isolation in people at high risk.

Free distribution of high-filtration masks
Despite controversies over masking, many people would voluntarily wear high-filtration masks in an epidemic. Stockpiles of N95s exist at the federal and state level. Contingency plans should be mapped out now so their supply and distribution could be quickly scaled if necessary.

Repair public trust
Immediate steps must be taken to address the lack of trust in medical and public health institutions among some people after the COVID-19 pandemic. This will be difficult after a heated US election, and during a surge of anti-vaccine sentiment, waning faith in public institutions and a polarized social media-driven information environment. Trust varies across localities and subpopulations; surveying attitudes across these groups could provide a granular, more sophisticated understanding of what needs to happen in different communities.

The COVID-19 pandemic also demonstrated that it is difficult for people to reliably adopt big changes amid the hysteria of an unfolding crisis. If the risk of an epidemic escalates, the public should be presented a clear picture of what is happening and what the plan to counter it is in advance of a full-fledged crisis. Public health proponents should also be ready to act with messaging designed to ‘prebunk’ anticipated misinformation and ‘socially inoculate’ people15.

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